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DUNSTON, JENNIFER ANN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 08/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/693,905	LAHTINEN ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50-129* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50-129* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 October 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/19/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.O.O

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 10/28/2003, in which claims 1-49 were canceled and claims 50-129 were newly added. Claims 50-129 are pending and under consideration in the instant application.

Receipt is acknowledged of an amendment, filed 8/2/2004, in which the specification was amended to comply with the sequence rules.

Information Disclosure Statement

Receipt of an information disclosure statement, filed on 5/19/2004, is acknowledged. The signed and initialed PTO 1449 has been mailed with this action.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It does not identify the citizenship of each inventor. The citizenship of Mika Lahtinen, Seppo Yla-Herttuala and Olli-Pekka Leppanen has not been provided.

Specification

The abstract of the disclosure is objected to because it contains legal phraseology such as "said nucleic acid" in line 5 of the abstract. Correction is required. See MPEP § 608.01(b).

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: Figure 1 contains reference characters a-n that are not described in the brief description of the drawings. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 66-81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 66 is vague and indefinite in that the metes and bounds of the phrase "composition comprising an extracellular superoxide dismutase" are unclear. It is unclear if the extracellular

superoxide dismutase is a protein or a nucleic acid molecule encoding an extracellular superoxide dismutase protein. The dependent claims refer back to "the nucleic acid" of claim 66; however, it is unclear if the composition comprises a nucleic acid. If the claim is amended to recite "a nucleic acid encoding extracellular superoxide dismutase," claims 66-73 would be objected to as being duplicates of claims 50-57.

Claim 68 recites the limitation "the nucleic acid" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 68 depends from claim 66, which recites "a composition comprising an extracellular superoxide dismutase." However, the composition of claim 66 is not limited to a nucleic acid encoding an extracellular superoxide dismutase.

Claim 69 recites the limitation "the nucleic acid" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 69 depends from claim 66, which recites "a composition comprising an extracellular superoxide dismutase." However, the composition of claim 66 is not limited to a nucleic acid encoding an extracellular superoxide dismutase.

Claim 70 recites the limitation "the nucleic acid" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 70 depends from claim 66, which recites "a composition comprising an extracellular superoxide dismutase." However, the composition of claim 66 is not limited to a nucleic acid encoding an extracellular superoxide dismutase.

Claim 74 is vague and indefinite in that the metes and bounds of the phrase "composition comprising an extracellular superoxide dismutase" are unclear. It is unclear if the extracellular superoxide dismutase is a protein or a nucleic acid molecule encoding an extracellular superoxide dismutase protein. The dependent claims refer back to "the nucleic acid" of claim 66; however, it is unclear if the composition comprises a nucleic acid. If the claim is amended to

recite "a nucleic acid encoding extracellular superoxide dismutase," claims 74-81 would be objected to as being duplicates of claims 58-65.

Claim 76 recites the limitation "the nucleic acid" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 76 depends from claim 74, which recites "a composition comprising an extracellular superoxide dismutase." However, the composition of claim 74 is not limited to a nucleic acid encoding an extracellular superoxide dismutase.

Claim 76 recites the limitation "the nucleic acid" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 76 depends from claim 74, which recites "a composition comprising an extracellular superoxide dismutase." However, the composition of claim 74 is not limited to a nucleic acid encoding an extracellular superoxide dismutase.

Claim 77 recites the limitation "the nucleic acid" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 77 depends from claim 74, which recites "a composition comprising an extracellular superoxide dismutase." However, the composition of claim 74 is not limited to a nucleic acid encoding an extracellular superoxide dismutase.

Claim 78 recites the limitation "the nucleic acid" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 78 depends from claim 74, which recites "a composition comprising an extracellular superoxide dismutase." However, the composition of claim 74 is not limited to a nucleic acid encoding an extracellular superoxide dismutase.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 50-129 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administering to a mammal a composition comprising a nucleic acid encoding extracellular superoxide dismutase, wherein the nucleic acid is in an adenoviral vector, does not reasonably provide enablement for any other method of delivering superoxide dismutase or the administration of any other nucleic acid sequence that leads to the production of extracellular superoxide dismutase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The claims are drawn to or encompass the step of administering to a mammal a composition comprising a nucleic acid encoding an extracellular superoxide dismutase. The amount of the nucleic acid administered must be sufficient to treat and/or prevent restenosis, treat and/or prevent blood vessel thickening, decrease macrophage accumulation, increase endothelial cell growth, or inhibit hyperplastic connective tissue growth. Further, the claims are drawn to or encompass the step of administering to a mammal a composition comprising a nucleic acid that encodes a gene product that leads to the production of extracellular superoxide dismutase protein. Thus, the nucleic acid may encode extracellular

superoxide dismutase or any other protein that may effect an increase in the production of endogenous extracellular superoxide dismutase.

The nature of the subject matter is complex, because the nucleic acid must be delivered at a level sufficient to produce a therapeutic outcome (see the discussion below).

Breadth of the claims: The claims are broad in that any vector may be used to deliver the nucleic acid encoding an extracellular superoxide dismutase. Further, the claims are broad because they encompass the administration of any nucleic acid encoding any protein that may effect an increase in the production of endogenous extracellular superoxide dismutase. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

State of the art: An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature, Vol. 389, pages 239-242, 1997; e.g. page 239, paragraph 1) and Palù et al (J. Biotechnol. Vol. 68, pages 1-13, 1999; e.g. Abstract) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al indicate that most approaches suffer from poor efficiency and transient expression of the gene (e.g. page 239, right column, paragraph 2). Likewise, Luo et al (Nature Biotechnology, Vol. 18, pages 33-37, 2000) indicate that non-viral synthetic delivery systems are very inefficient (e.g. Abstract; page 33, left column, paragraphs 1 and 2). Regarding viral methods for gene delivery *in vivo*, Verma et al, indicate that lentiviral, adenoviral and AAV vectors are capable of

delivery genes, but there is a possibility for insertional mutagenesis or toxicity due to an inflammatory response (e.g. Table 2).

French et al (US Patent No. 6,290,949) teach that the concept of direct gene transfer to inhibit restenosis was first articulated in the context of retrovirus- and lipofectin-mediated gene transfer; however, the absolute level of recombinant protein produced *in vivo* by these techniques was to low to be considered therapeutically significant (e.g. column 10, lines 43-50). Further, French et al teach that ventricular myocytes do not divide, and thus retroviral vectors cannot be employed to deliver therapeutic nucleic acid molecules to the cardiac muscle cells (e.g. column 12, lines 48-63). Further, Kotani et al (Current Gene Therapy, Vol. 4, No. 2, pages 183-194, 2004) teach that naked plasmid DNA is generally unstable because it is taken up by endocytosis and is rapidly degraded in the lysosome (e.g. page 183, paragraph bridging columns).

With regard to Sendai virus vectors, Kotani et al teach that the envelope hemagglutinating virus or Japan (HVJ or Sendai virus) rather than the viral genome is a promising gene therapy vector with low toxicity and immunogenicity (e.g. page 188, right column; Table 2). However, there is no precedent case of clinical applications (Kotani, 2004; e.g. paragraph bridging pages 191-192). Systemic safety and toxicology studies are required for the clinical use of HVJ envelope vectors (Kotani, 2004; e.g. paragraph bridging pages 191-192).

With regard to xenografts in the treatment of cardiac disease, Platt teaches that the main hurdle to clinical application is the immune response of the recipient against the graft (e.g. Abstract). Xenografts may be subject to primary non-function, failure of neovascularization, failure of the microenvironment to support the tissue, acute vascular rejection or hyperacute rejection (e.g. Figure 1).

Predictability of the art: The area of the invention is unpredictable. As discussed above, the method of *in vivo* gene therapy is highly complex and unpredictable. Indeed, recent gene therapy protocols have demonstrated unpredictable outcomes resulting from an unexpected inflammatory reaction to an adenoviral vector in a patient and the insertional mutagenesis of a gene resulting in a leukemia-like condition in children being treated for severe combined immunodeficiency (Edelstein et al, J. Gene Med. Vol. 6, pages 597-602, 2004; e.g. page 599, The hopes and the setbacks). The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect.

Guidance of the specification and existence of working examples: The specification teaches that trauma to the blood vessel endothelium results in the formation of excessive connective tissue and inflammatory reaction and subsequent occlusion because of thrombosis or restenosis (e.g. page 4, lines 1-3; paragraph bridging pages 10-11). To address these physiologic response to trauma, the specification broadly envisions the administration of a nucleic acid encoding an extracellular superoxide dismutase (EC-SOD), EC-SOD protein, a protein that results in increased EC-SOD or a nucleic acid encoding a protein that results in increased EC-SOD (e.g. paragraph bridging pages 11-12). The specification envisions the local or systemic administration of the nucleic acid encoding EC-SOD in the form of naked nucleic acid, in a viral vector such as a retrovirus, Sendai virus, lentivirus, adeno-associated virus or adenovirus, in a liposome, or in an artificial chromosome (e.g. page 13, lines 5-20; pages 22-23; pages 27-28).

The specification does not teach how to make and use any nucleic acid encoding any protein that is capable of increasing the expression of endogenous EC-SOD. The only nucleic

acid sequence taught by the specification that is capable of increasing EC-SOD protein is the EC-SOD nucleic acid sequence (e.g. paragraph bridging pages 32-33). The specification provides little or no guidance with regard to other nucleic acid sequences or proteins that can stimulate endogenous EC-SOD production or activity. Further, the specification does not overcome the limitations of the use of naked DNA or viral vectors such as retroviruses, Sendai virus or adeno-associated virus to achieve therapeutic expression of EC-SOD. Further, the specification states the following with regard to retroviral vectors:

> Retroviruses have several drawbacks *in vivo* which limit their usefulness. They provide stable gene transfer, but current retroviruses are unable to transduce replicating cells. The potential hazards of transgene incorporation into the host DNA are not warranted if short-term gene transfer is sufficient. See page 22, lines 25-29.

The specification does not provide any working examples that demonstrate the systemic safety of any Sendai virus vector.

The claims read on the administration of a composition comprising cell containing a nucleic acid encoding EC-SOD (i.e. *ex vivo* gene therapy). The specification contemplates the administration of xenografts, allografts or autografts as tissue sources for *ex vivo* gene therapy (e.g. paragraph bridging pages 58-59). The specification does not teach the expression of EC-SOD in xenogeneic tissues sufficient to overcome the immune system mediated rejection of xenogeneic tissues. Further, the specification does not disclose any working examples that teach the administration of cells, either xenogeneic, allogenic or autogenic, that express EC-SOD and are capable of treating and/or preventing restenosis, treating and/or preventing blood vessel

thickening, decreasing macrophage accumulation, increasing endothelial cell growth, or inhibiting hyperplastic connective tissue growth.

The working example discloses the administration to a rabbit stenosis model an adenoviral vector comprising a rabbit lung cDNA encoding EC-SOD (e.g. pages 63-65). Adenoviral vector ($3x10^9$ pfu/kg) was administered three days after the denudation of aortic endothelium (e.g. page 65, lines 3-13). The administration of the adenoviral vector encoding EC-SOD resulted in a significant reduction in neointima formation with a reduction in macrophage infiltration (e.g. page 66, lines 11-23; page 67, lines 11-27). Further, the EC-SOD treated group had significantly more endothelial recovery (e.g. paragraph bridging pages 66-67).

Amount of experimentation necessary: The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to make and use the claimed methods commensurate in scope with the claims. The successful outcome observed with the adenoviral vector encoding an EC-SOD protein is not necessarily predictive of the outcome when other vectors or nucleic acid sequences are used. In order to determine how to use the method to treat the claimed conditions, one of skill in the art would have to identify nucleic acid sequence capable of stimulating EC-SOD production or activity. With any nucleic acid one would have to determine how to deliver the given nucleic acid (e.g. EC-SOD or another nucleic acid) to the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 50-129 are not considered to be fully enabled by the instant specification.

Claims 82-129 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to the step of administering a nucleic acid that encodes a translation or transcription product that leads to the production of extracellular superoxide dismutase protein (EC-SOD). Thus, the claims encompass the step of providing a set of nucleic acid molecules encoding proteins that increase the production of EC-SOD. The claims do not provide any structural information with regard to the sequences capable of increasing the production of EC-SOD. Thus, the rejected claims thus comprise a set of nucleic acid sequences that are defined by the function of the encoded protein.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification describes the coding sequence of EC-SOD (e.g.

paragraph bridging pages 32-33). No description is provided of any other sequence that results in the production of a protein that increases the production of EC-SOD.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of one nucleic acid sequence capable of increasing the production of EC-SOD. The results are not necessarily predictive of any other sequence capable of increasing the production of EC-SOD. Thus, it is impossible for one to extrapolate from the example described herein those nucleic acid molecules that would necessarily meet the structural/functional characteristics of the rejected claims.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe a set of genes or proteins that regulate the production of EC-SOD. Marklund et al (WO 96/14060) describe proteins capable of increasing EC-SOD synthesis in arterial smooth muscle cells (e.g. page 8, lines 1-15; Table 4). However, the fold increase in EC-SOD levels after exposing cells to the effector proteins was only moderate with only a few substances eliciting greater than a 3-fold increase in EC-SOD (see *Predictability of the art*, above). Given the limitations with regard to efficient gene expression in the context of gene therapy, one could expect a reduction in EC-SOD expression relative to the teachings of Marklund et al.

Given the very large genus of nucleic acid molecules encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to the sequences capable of inducing the production of EC-SOD, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus of nucleic acid sequences capable

of inducing the production of EC-SOD. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those nucleic acid sequences that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention for claims 82-129.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 66, 67, 72-75, 80, 81, 98, 99, 104-107, 112-115, 120-123, 128 and 129 are rejected under 35 U.S.C. 102(b) as being anticipated by Marklund et al (US Patent No. 5,366,729; see the entire reference) as evidence by French (US Patent No. 6,290,949).

Regarding claims 66, 74, 98, 106, 114 and 122, Marklund et al teach the administration of a pharmaceutical composition comprising a polypeptide having superoxide dismutating property of native EC-SOD in a therapeutically effective dose (e.g. column 31, lines 25-68). Further, Marklund et al claim a method for preventing or treating a disorder at least in part caused by or exacerbated by the presence or formation of superoxide radicals, wherein the disorder is damage caused by ischemia followed by reperfusion, or in connection with the

transplantation of organs selected from the group consisting of kidney, lung, pancreas, liver, skin, bone tissue, extremities, skeletal muscle, lens, and cornea, or in connection with heart surgery, comprising administering a therapeutically or prophylactically effective amount of a polypeptide or a polypeptide composition comprising a non-naturally occurring EC-SOD-like polypeptide of claim 1 before, during or after surgery (claims 1 and 14).

Regarding claims 67, 75, 99, 107, 115 and 123, Marklund et al teach the systemic administration of the EC-SOD protein (e.g. column 31, lines 35-68).

Regarding claims 72, 80, 104, 112, 120 and 128, Marklund et al teach repeated administration of the EC-SOD protein at a dosage of about 15-600 mg/day (e.g. column 31, lines 35-68).

Regarding claims 73, 81, 105, 113, 121 and 129, Marklund et al teach the treatment of a human with EC-SOD polypeptide (e.g. column 31, lines 35-68).

The claims read on the teachings of Marklund et al because Marklund et al teach the claimed method step of administering an EC-SOD polypeptide. The patient population that Marklund et al teach are individuals that have a myocardial infarction (e.g. columns 25-26). French et al (the '949 patent) teach that restenosis can occur incident to myocardial infarction (e.g. paragraph bridging columns 6-7). Thus, the patient population taught by French encompasses a patient population at risk for or with restenosis. Marklund et al teach the use of a therapeutically effective dose to treat myocardial infarction or ischemia/reperfusion injury. Thus, the administration of an EC-SOD polypeptide as taught by Marklund et al inherently results in treating and/or preventing restenosis, treating and/or preventing blood vessel thickening, decreasing macrophage accumulation, increasing endothelial cell growth, and

inhibiting hyperplastic connective tissue growth. Therefore, absent any evidence to the contrary, the skilled artisan would necessarily expect that administration of an EC-SOD polypeptide to an individual, as taught by Marklund et al, would result in the claimed invention.

Claims 50-53, 57-61, 65-59, 73-77, 81-85, 89-92, 97-101, 105-108, 113-117, 121-125 and 129 are rejected under 35 U.S.C. 102(e) as being anticipated by French (US Patent Application Publication No. 2002/0061299; see the entire reference) as evidenced by French (US Patent No. 6,290,949).

The claims are drawn to or encompass the step of administering to a mammal a composition comprising a nucleic acid encoding an extracellular superoxide dismutase. The amount of the nucleic acid administered must be sufficient to treat and/or prevent restenosis, treat and/or prevent blood vessel thickening, decrease macrophage accumulation, increase endothelial cell growth, or inhibit hyperplastic connective tissue growth.

Regarding claims 50, 58, 66, 74, 82, 90, 98, 106, 114 and 122, French teaches the administration of a recombinant adenovirus (Ad5) gene therapy vector comprising a nucleic acid sequence encoding extracellular superoxide dismutase (EC-SOD) to a mammal to treat ischemia/reperfusion injury such as myocardial infarction (e.g. paragraphs [0007], [0008], [0024]-[0028], [0035], [0043], [0045]). Further, French teaches a sufficient quantity of gene therapy vector to achieve systemic elevations in EC-SOD therapeutic protein (e.g. paragraph [0008]).

Regarding claims 51, 59, 67, 75, 83, 91, 99, 107, 115 and 123, French teaches the administration of the adenoviral vector comprising a nucleic acid encoding EC-SOD by systemic or local delivery (e.g. paragraph [0008]).

Regarding claims 52, 60, 68, 76, 84, 92, 100, 108, 116 and 124, French teaches the administration of the nucleic acid encoding EC-SOD in plasmid (i.e. naked) form (e.g. paragraphs [0007], [0008], [0024]-[0028], [0035], [0043], [0045], claims 1, 2 and 5).

Regarding claims 53, 61, 69, 77, 85, 93, 101, 109, 117 and 125, French teaches the delivery of the EC-SOD nucleic acid in an adenoviral vector or an adeno-associated virus (e.g. paragraphs [0007], [0008], [0024]-[0028], [0035], [0043], [0045], claims 1-4).

Regarding claims 57, 65, 73, 81, 89, 97, 105, 113, 121 and 129, French demonstrates the utility of the gene therapy method in a rabbit model (e.g. paragraphs [0021]-[0028]). French teaches that the rabbit model closely mimics the human condition of a heart attack (e.g. paragraph [0006]). Further, French et al teach the use of the human cDNA encoding EC-SOD (e.g. paragraph [0024]). Moreover, French envision the treatment of any patient (e.g. claim 1). Thus, French teaches the administration of a nucleic acid encoding EC-SOD to a human patient.

The claims read on the teachings of French because French teaches the claimed method step of administering a nucleic acid encoding an extracellular superoxide dismutase. The patient population that French teaches are individuals that have or could potentially have a myocardial infarction (e.g. Abstract; paragraph [0008]). French et al (the '949 patent) teach that restenosis can occur incident to myocardial infarction (e.g. paragraph bridging columns 6-7). Thus, the patient population taught by French encompasses a patient population at risk for or with restenosis. As disclosed in the instant specification, an adenoviral vector comprising a nucleic

acid encoding EC-SOD administered at a dosage of $3x10^9$ pfu/kg is sufficient to induce a therapeutic effect. This dosage is similar to the dosage of $2x10^8$ pfu/kg taught by French. Further, French teaches that the dosage used was capable of increasing SOD activity in the heart 5.4-fold. Thus, the administration of a nucleic acid encoding extracellular superoxide dismutase as taught by French inherently results in treating and/or preventing restenosis, treating and/or preventing blood vessel thickening, decreasing macrophage accumulation, increasing endothelial cell growth, and inhibiting hyperplastic connective tissue growth. Therefore, absent any evidence to the contrary, the skilled artisan would necessarily expect that administration of a nucleic acid encoding an extracellular superoxide dismutase to an individual, as taught by French, would result in the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 50-129 are rejected under 35 U.S.C. 103(a) as being unpatentable over French et al (US Patent No. 6,290,949; see the entire reference) in view of French (US Patent Application Publication No. 2002/0061299; see the entire reference).

The claims are drawn to or encompass the step of administering to a mammal a composition comprising a nucleic acid encoding an extracellular superoxide dismutase. The amount of the nucleic acid administered must be sufficient to treat and/or prevent restenosis, treat and/or prevent blood vessel thickening, decrease macrophage accumulation, or increase endothelial cell growth.

Regarding claims 50, 58, 66, 74, 82, 90, 98, 106, 114 and 122, French et al (the '949 patent) teach the administration to a mammal a composition comprising a nucleic acid encoding superoxide dismutase (SOD) for the treatment of restenosis, treatment and/or inhibition of intimal thickening, (e.g. column 4, lines 49-67; column 5, lines 1-59; column 11, lines 10-35; column 12, lines 35-46; Example 8; claims 1-7). Absent any evidence to the contrary, the level of superoxide dismutase nucleic acid delivered to treat restenosis and to inhibit intimal thickening would also be sufficient to decrease macrophage accumulation and increase endothelial cell growth.

Regarding claims 51, 59, 67, 75, 83, 91, 99, 107, 115 and 123, French et al teach the administration of the adenoviral vector comprising a nucleic acid encoding EC-SOD by systemic or local delivery (e.g. column 17, line 32, to column 18, line 30; column 27, lines 20-50).

Regarding claims 52, 60, 68, 76, 84, 92, 100, 108, 116 and 124, French et al teach the administration of the nucleic acid encoding SOD in plasmid (i.e. naked) form (e.g. column 13, lines 38-47).

Regarding claims 53, 61, 69, 77, 85, 93, 101, 109, 117 and 125, French et al teach the delivery of the SOD nucleic acid in an adenoviral vector (e.g. column 13, line 36, to column 15, line 52)

Regarding claims 54, 62, 70, 78, 86, 94, 102, 110, 118 and 126, French et al teach the delivery of the SOD nucleic acid in a liposome (e.g. column 4, line 65, to column 5 line 23).

Regarding claims 55, 63, 71, 79, 87, 95, 103, 111, 119 and 127, French et al teach the delivery of the SOD nucleic acid in a biostable polymer, bioabsorbable polymer, a biomolecule, or a hydrogel polymer (column 18, lines 8-30).

Regarding claims 56, 64, 72, 80, 88, 96, 104, 112, 120 and 128, French et al teach that the administration of a nucleic acid encoding SOD in the form of a replication-deficient adenovirus has a finite lifespan before it is degraded by host nucleases; therefore, it is ideally designed to treat acute conditions such as restenosis (e.g. column 14, lines 55-57). Because acute conditions such as restenosis can occur in the same individual more than once, it would be obvious to administer repeat the administration of the nucleic acid encoding SOD at least once.

Regarding claims 57, 65, 73, 81, 89, 97, 105, 113, 121 and 129, French et al teach the administration of the nucleic acid encoding SOD to humans (e.g. column 6, lines 10-20).

French et al do not teach the administration of a nucleic acid encoding the extracellular form of SOD.

French (2002/0061299) teaches the administration of a recombinant adenovirus (Ad5) gene therapy vector comprising a nucleic acid sequence encoding extracellular superoxide dismutase (EC-SOD) to a mammal to treat ischemia/reperfusion injury such as myocardial infarction (e.g. paragraphs [0007], [0008], [0024]-[0028], [0035], [0043], [0045]). Further, French teaches a sufficient quantity of gene therapy vector to achieve systemic elevations in EC-SOD therapeutic protein (e.g. paragraph [0008]). Moreover, French teaches that the extracellular isoform of SOD has natural affinity for the interstitial space and that the interstitial levels of SOD (rather than the plasma levels) are primarily responsible for protection against ischemia/reperfusion injury (e.g. paragraph [0037]). EC-SOD binds to heparin sulfate proteolysis present on the endothelial glycocalyx, in the extracellular matrix, and on the sarcolemma of cardiomyocytes, thereby providing effective protection against oxygen radicals in the interstitium and vulnerable cellular surfaces (e.g. paragraph [0044]).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of administering a nucleic acid encoding SOD of French et al (the '949 patent) to include the EC-SOD coding sequence taught by French (2002/0061299) because French et al and French teach it is within the ordinary skill in the art to use SOD to administer a nucleic acid encoding SOD to a patient. Further, it would have been obvious to repeat the administration of the nucleic acid encoding EC-SOD at least once because French et al teach that the nucleic acid will be degraded, and one patient may need treatment for acute restenosis more than once.

One would have been motivated to make such a modification in order to receive the expected benefit of using a more efficient SOD as taught by French (2002/0061299). French

teaches that EC-SOD is more efficient because it binds to heparin sulfate proteolysis present on the endothelial glycocalyx, in the extracellular matrix, and on the sarcolemma of cardiomyocytes, thereby providing effective protection against oxygen radicals in the interstitium and vulnerable cellular surfaces. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jennifer Dunston
Examiner
Art Unit 1636

jad

TERRY MCKELVEY
PRIMARY EXAMINER